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New chiral diazapyridino-18-crown-6 macrocycles **1-5** (Figure 1) have been prepared. Cyclization of chiral diols **6-10** containing two methyl or two benzyl substituents or both two methyl and two phenyl substituents with 2,6-pyridinedimethyl ditosylate in the presence of sodium hydride gave the symmetrical macrocyclic ligands **1-5**. **1-5** have three equally spaced nitrogen atoms in the ring which should form ideal tripod hydrogen bonds with chiral organic ammonium salts.

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New chiral diazapyridino-18-crown-6 macrocycles **1-5** (Figure 1) have been prepared. Cyclization of chiral diols **6-10** containing two methyl or two benzyl substituents or both two methyl and two phenyl substituents with 2,6-pyridinedimethyl ditosylate in the presence of sodium hydride gave the symmetrical macrocyclic ligands **1-5**. **1-5** have three equally spaced nitrogen atoms in the ring which should form ideal tripod hydrogen bonds with chiral organic ammonium salts.

INTRODUCTION

The factors which affect enantiomeric recognition by pyridine-containing chiral crown ethers for chiral organic ammonium salts have been systematically studied. The results of these studies have increased our understanding of how the extent of enantiomer recognition varies with crown substituent, functional group type, guest type, solvent and donor atom type[1,2]. In general, solvents can significantly change complex stabilities. In some cases, solvents can also change the extent of enantiomeric recognition[3]. Substitutents and functional groups on the crown ethers have significant affects on complex stabilities and enantiomeric recognition[1,2]. Donor atoms in the ring can affect the tripod hydrogen bonding by altering the strength of the hydrogen bonds. The importance of tripod hydrogen bonds has been illustrated in our previous work[1]. Generally speaking, nitrogen atoms form stronger hydrogen bonds than oxygen atoms[4]. When both oxygen and nitrogen atoms are in the macrocyclic ring, only the nitrogen atoms form hydrogen bonds with ammonium salts. It has been confirmed from crystal structures that the tripod hydrogen bonding between the pyridino-18-crown-6 ligands and various primary ammonium salts does involve the pyridine nitrogen atom[5,6]. The nitrogen atom of an azapyridino-18-crown-6 ligand are favored over ring oxygen atoms in forming hydrogen bonds to an ammonium ion[7]. On the other hand, full use of nitrogen atoms requires their proper arrangement in the ring in order to allow the three hydrogen bonds to be formed between the ring nitrogen atoms and hydrogen atoms of an ammonium salt. Ideal placement is to have the nitrogen atoms in alternate heteroatom positions in the ring. Improper location of nitrogen atoms could lead to reduced complexation and poor enantiomeric recognitions.

In order to investigate the effect of the tripod hydrogen bonding on complex stabilities and enantiomeric recognition, chiral diazapyridino-18-crown-6 ligands **1-5** have been prepared. Compounds **1-5** have three alternate nitrogen atoms in the ring which will, hopefully, form ideal tripod hydrogen bonds with chiral organic ammonium salts.

Results and Discussion

New chiral macrocycles **1-5** (see Figure 1) were prepared as shown in Scheme 1. Cyclization of the appropriate chiral diols **6-10** with 2,6-pyridinedimethyl ditosylate in the presence of sodium hydride gave the symmetrical chiral diazapyridino-18-crown-6 ligands **1-5**. The structures proposed for compounds **1-5** and were are consistent with data obtained from their ^{1}H NMR, MS and IR spectra and elemental analyses.

Chiral dialkyl-substituted diazatetraethylene glycols needed for the preparation of the chiral macrocycles were obtained as shown in Scheme II. Compounds **6-10** were formed by treatment of the appropriate chiral amino alcohols **16-20** with diglycolyl chloride in the presence of triethylamine in dichloromethane to give intermediates **11-15**. Diamide intermediates **11-13** and **15** were reduced using $LiAlH_4$ to give diazatetraethylene glycols **6-8** and **10** in overall yields of 11-52% (Scheme IIA). Diamide intermediate **14** was purified by recrystallization and then reduced with B_2H_6 to give compound **9** in a 47% yield (Scheme IIB). Diamines **6-10** were used to prepare the macrocycles (Scheme I) using a strong base which deprotonated the alcohol functions to allow them to act as the nucleophiles[8].

Macrocycles **1-5** were prepared to deterimine if alternate nitrogen donor atoms in the chiral pyridino-18-crown-6 macroring would improve both its interactive ability and selectivity for the enantiomers of chiral organic ammonium salts. Compexation studies are in progress and will be reported when that work is finished.

Experimental

The ^1H NMR spectra were obtained at 200 MHz in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard (for structural determinations). Melting points were not corrected. Starting materials were used as purchased from Aldrich Chemical Co. unless otherwise noted. 2,6-Pyridinedimethyl ditosylate was prepared as reported[9-12].

(4*R*,14*R*)-(-)-4,14-Dimethyl-3,9,15-trioxa-6,12,21-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, **1** (Scheme I).

To a stirred suspension of 1.12 g (28 mmol, 60% dispersion in mineral oil) of NaH in 40 ml of dry THF was added dropwise, 1.44 g (6.5 mmol) of **6** dissolved in 100 ml of THF under nitrogen at room temperature. The reaction mixture was heated to reflux for 3 h. The mixture was cooled to 0 °C and 2.92 g (6.5 mmol) of 2,6-pyridinedimethyl ditosylate in 200 ml of THF was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 3 days. After the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 300 ml of CH_2Cl_2, 50 g of ice and 50 ml of H_2O. The mixture was shaken well and separated. The aqueous phase was extracted three times with 100-ml portions of CH_2Cl_2. The combined organic phases were

dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/150) as eluant to give 0.84 g (25%) of **1** as a yellow oil; $[\alpha]_D$-41.50 (c = 0.20, $CHCl_3$); IR (neat) 3320, 2965, 2876, 1593, 1578, 1456, 1373, 1345, 1115, 794, 763 cm^{-1}; ^1H NMR ($CHCl_3$) δ 1.22 (d, 6H), 1.30-2.20 (b, 2H, disappeared on addition of D_2O), 2.55-2.85 (m, 8H), 3.44 (s, 2H, disappeared on addition of D_2O), 3.46-3.64 (m, 4H), 3.65-3.85 (m, 2H), 4.50-4.80 (q, 4H), 7.22 (d, 2H), 7.65 (t, 1H); MS *m/e* 324 (M^+ + 1). *Elem. anal.*, found % (calcd for $C_{17}H_{29}N_3O_3$): C, 63.34 (63.16); H, 9.05 (9.14).

(5*R*,13*R*)-(-)-5,13-dimethyl-3,9,15-trioxa-6,12,21-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, **2** (Scheme I).

Compound **2** was prepared as described above for **1** using 1.44 g (6.5 mmol) of **7**, 1.12 g (28 mmol, 60% dispersion in mineral oil) of NaH and 2.92 g (6.5 mmol) of 2,6-pyridinedimethyl ditosylate. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/100) as eluant to give 0.53 g (25%) of **2** as a yellow oil; $[\alpha]_D$-22.78 (c = 0.16, $CHCl_3$); IR (neat) 3329, 2963, 2866, 1593, 1578, 1457, 1370, 1351, 1267, 1234, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 6H), 2.05 (s, 2H, disappeared on addition of D_2O), 2.72-3.02 (m, 6H), 3.30-3.62 (m, 8H), 4.59 (s, 4H), 7.30 (d, 2H), 7.65 (t, 1H); MS *m/e* 324 (M^+ + 1). *Elem. anal.*, formed % (calcd for $C_{17}H_{29}N_3O_3$): C, 63.00 (63.16); H, 8.73 (9.04).

(5*R*,13*R*)-(-)-5,13-dibenzyl-3,9,15-trioxa-6,12,21-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, **3** (Scheme I).

Compound **3** was prepared as described above for **1** using 0.74 g (2.0 mmol) of **8**, 0.36 g (9 mmol, 60% dispersion in mineral oil) of NaH and 0.9 g (2.0 mmol) of 2,6-pyridinedimethy ditosylate. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/500) as eluant to give 0.28 g (30%) of **3** as a yellow oil: $[\alpha]_D$-27.7 (c = 0.44, C_6H_6); IR (neat) 3328, 2858, 1594, 1578, 1495, 1455, 1349, 1118, 1030, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (b, 2H, disappeared on addition of D_2O), 2.60-2.90 (m, 8H), 2.90-3.08 (m, 2H), 3.32-3.58 (m, 8H), 4.52 (s, 4H), 7.08-7.35 (m, 12H), 7.54-7.64 (t, 1H); MS *m/e* 476 (M^+ + 1). *Elem. anal.*, found % (calcd for $C_{29}H_{37}N_3O_3$): C, 73.12 (73.25); H, 7.55 (7.84).

(5*S*,13*S*)-(+)-5,13-dibenzyl-3,9,15-trioxa-6,12,21-triazabicyclo-[15.3.1]heneicosa-1(21),17,19-triene, **4** (Scheme I).

Compound **4** was prepared as described above for **1** using 0.74 g (2.0 mmol) of **9**, 0.36 g (9 mmol, 60% dispersion in mineral oil) of NaH and 0.90 g (2.0 mmol) of 2,6-pyridinedimethyl ditosylate. The crude product was purified by chromatography on silica gel using 30% aqueous NH_4OH/CH_3OH (1/300) as eluant to give 0.35 g (36%) of **4** as a yellow oil: $[\alpha]_D$+28.30 (c = 0.11, C_6H_6); IR(neat) 3328, 2858, 1594, 1495, 1455, 1349, 1118, 1030, 748, 701 cm^{-1};^1H NMR ($CDCl_3$) δ 1.52(b, 2H, disappeared on addition of D_2O), 2.60-2.90 (m, 8H), 2.90-3.08 (m, 2H), 3.32-3.58 (m, 8H), 4.59 (s, 4H), 7.08-7.35 (m, 12H), 7.62 (t, 1H); MS *m/e* 475(M^+). *Elem. anal.*, found % (calcd for $C_{29}H_{37}N_3O_3$): C, 73.28 (73.25); H, 7.64 (7.84).

(4*R*,5*S*,13*S*,14*R*)-(+)-5,13-dimethyl-4,14-diphenyl-3,9,15-trioxa-6,12,21-triazabicyclo[15.3.1]heneicosa-1(21),17,19-triene, **5** (Scheme I).

Compound **5** was prepared as described above for **1** using 0.74 g (2.0 mmol) of **10**, 0.36 g (9 mmol, 60% dispersion in mineral oil) of NaH and 0.9 g (2.0 mmol) of 2,6-pyridinedimethyl ditosylate. The crude product was purified by chromatography on silica gel using CH_3OH as eluant to give 0.16 g (17%) of **5** as a yellow oil: $[\alpha]_D$+83.97 (c = 0.16, $CHCl_3$); IR (neat) 3322, 3060, 3029, 2876, 1592, 1451, 1352, 1117, 747, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 6H), 1.83-2.10 (b, 2H, disappeared on addition of D_2O), 2.50-2.90 (m, 6H), 3.50-3.60 (t, 4H), 4.50-4.85 (q, 4H), 4.73 (d, 2H), 7.20-7.45 (m, 12H), 7.67 (t, 1H); MS *m/e* 477(M^+ + 1). *Elem. anal.* found % (calcd for $C_{29}H_{37}N_3O_3$): C, 73.12 (73.25); H, 7.59 (7.84).

(1*R*,11*R*)-(+)-1,11-Dimethyl-3,9-diaza-6-oxaundecane-1,11-diol, **6** (Scheme IIA).

A solution of 5.40 g (0.03 mol) of diglycolyl chloride in 300 ml of CH_2Cl_2 was added to a stirred mixture of 6.08 g (0.06 mol) of (*R*)-(-)-1-amino-2-propanol and 6.08 g (0.06 mol) of triethylamine at 0 °C over a period of 10 h. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. The CH_2Cl_2 was removed under reduced pressure and the residue was partially dissolved in 50 ml of DMF. The suspended white solid was removed by filtration and washed with DMF. The combined filtrate and washings were evaporated under reduced pressure to give crude diamide **11** which was reduced without further purification.

A solution of crude diamide **11** in 150 ml of dry THF was cautiously added to 8.0 g (0.21 mol) of $LiAlH_4$ at room temperature. The reaction mixture was heated at reflux for two

days. Water (4 ml) and then 5% NaOH solution (10 ml) were added very slowly with stirring at 0 °C to destroy the excess $LiAlH_4$. After stirring for 1 h and then standed overnight, the suspended solid was removed by filtration and washed with THF . The combined filtrate and washings were evaporated under reduced pressure to give the crude product. This product was recrystallized from $CHCl_3$/diethyl ether (1/5) to give 2.04 g (31% overall) of **6** as white crystals; mp 70.5-71.0 °C; $[\alpha]_D$+50.6 (c = 0.51, $CHCl_3$); IR (KBr) 3115, 2963, 2882, 1653, 1431, 1156, 1109, 1102, 944 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 6H), 2.40-2.95 (m, 8H), 3.10 (s, 4H, disappeared on addition of D_2O), 3.58 (t, 4H), 3.85 (m, 2H); MS *m/e* 221 (M^+ + 1). A satisfactory elemental analysis was obtained for **1**, a derivative of **6**.

(2*R*,10*R*)-(+)-2,10-Dimethyl-3,9-diaza-6-oxaundecane-1,11-diol, **7** (Scheme IIA).

Compound **7** was prepared as described above for **6** using 4.60 g (0.06 mol) of (*R*)-(-)-2-amino-1-propanol in the place of (*R*)-(-)-1-amino-2-propanol, 5.40 g (0.03 mol) of diglycolyl chloride, 6.08 g (0.06 mol) of triethylamine and 8.0 g (0.21 mol) of $LiALH_4$. The crude product was purified by recrystallization from ethyl acetate to give 2.69 g (41% overall) of **7** as white crystals; mp 84.0-85.0 °C; $[\alpha]_D$= +67.6 (c = 0.93, $CHCl_3$); IR(KBr) 3119, 2849, 1647, 1431, 1378, 1247, 1112, 1058 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 6H), 2.80-3.00 (m, 6H), 3.40-3.70 (m, 12H, 4H disappeared on addition of D_2O); MS *m/e* 221(M^+ + 1). A satisfactory elemental analysis was obtained for **2**, a derivative of **7**.

(2*R*,10*R*)-(+)-2,10-Dibenzyl-3,9-diaza-6-oxaundecane-1,11-diol, **8** (Scheme IIA).

Compound **8** was prepared as described above for **6** using 4.90 g (0.035 mol) of (*R*)-(+)-2-amino-3-phenyl-1-propanol in the place of (*R*)-(-)-1-amino-2-propanol, 3.15 g (0.0175

mol) of diglycolyl chloride, 3.54 g (0.035 mol) of triethylamine and 4.0 g (0.105 mol) of $LiAlH_4$. The crude product was recrystallized from $CHCl_3$ to give 1.54 g (31% overall) of **8** as white crystals; mp 100.0-100.5 °C; $[\alpha]_D$+7.44 (c = 0.12, C_6H_6); IR(KBr) 3448, 2919, 2848, 1451, 1117, 1095, 1078 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.60 (s, 2H, disappeared on addition of D_2O), 2.55-2.80 (m, 10H), 3.12-3.40 (m, 8H), 4.50 (t, 2H, disappeared on addition of D_2O); MS *m/e* 373(M^+ + 1). A satisfactory elemental analysis was obtained for **3**, a derivative of **8**.

(2*S*,10*S*)-(-)-2,10-Dibenzyl-4,8-dicarbonyl-3,9-diaza-6-oxaundecane-1,11-diol, **14** (Scheme IIA).

A solution of 2.57 g (0.15 mol) of diglycolyl chloride in 100 ml of CH_2Cl_2 was added to a stirred mixture of 4.54 g (0.03 mol) of (*S*)-(-)-2-amino-3-phenyl-1-propanol and 3.04 g (0.03 mol) of triethylamine at 0 °C over a period of 10 h. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. The CH_2Cl_2 was evaporated under reduced pressure and the residue was partially dissolved in 50 ml of DMF. The suspended white solid was removed by filtration and washed with DMF. The combined filtrate and washings were evaporated under reduced pressure to yield a crude diamide. The crude product was purified by recrystallization from $CHCl_3$/petroleum ether (1/1) to give 2.60 g (43%) of **14** as white crystals; mp 88.0-90.0 °C; $[\alpha]_D$-25.64 (c = 0.55, $CHCl_3$); IR(KBr) 3288, 1640, 1548, 1138, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, 2H, disappeared on addition of D_2O), 2.89 (s, 4H), 3.02-3.18 (m, 2H disappeared on addition of D_2O), 3.50-3.71 (m, 4H), 3.92 (d, 4H), 4.10-4.32 (m, 2H), 7.08-7.38 (m, 10H); MS *m/e* 401(M^+ + 1).

(2*S*,10*S*)-(-)-2,10-Dibenzyl-3,9-diaza-6-oxaundecane-1,11-diol, **9** (Scheme IIB).

A 1 M THF solution (98 ml) of borane was added to a suspension of 2.0 g (4.9 mmol) of **14** in 30 ml of THF in a nitrogen atmosphere. The resulting reaction mixture was heated at reflux for two days. After cooling to 0 °C, water (3 ml) was added cautiously to destroy the excess borane. The solvent was evaporated under reduced pressure. Aqueous HCl (37%, 60 ml), water (60 ml) were added to the residue. The reaction mixture was stirred at room temperature for one day followed by 2 h at 70 °C. A portion of the water was evaporated and 30% aqueous ammonia solution was added until the pH was 13. The precipitated solid was removed by filtration and washed with water. The combined filtrate and washings were saturated with NaCl and extracted with CH_2Cl_2 four times. The combined organic phases were dried ($MgSO_4$), filtrated and evaporated under reduced pressure. The crude product was purified by recrystallization from $CHCl_3$ to give 0.86 g (47%) of **9** as white crystals; mp 99.0-99.5 °C; $[\alpha]_D$-7.02 (c = 0.11, C_6H_6); IR (KBr) 3461, 2912, 2841, 1451, 1110, 1090, 1065 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.55-2.80 (m, 10H), 3.20-3.40 (m, 8H), 3.50-4.50(b, 4H, disappeared on addition of D_2O), 7.12-7.34 (m, 10H); MS *m/e* 373 (M^+ + 1). The satisfactory elemental analysis was obtained for **4**, a derivative of **9**.

(1*S*,2*R*,10*R*,11*S*)-(+)-1,11-Diphenyl-2,10-dimethyl-3,9-diaza-6-oxaundecane-1,11-diol, **10** (Scheme IIA).

Compound **10** was prepared as described above for compound **6** using 4.54 g (0.03 mol) of (1*S*,2*R*)-(+)-2-amino-1-phenyl-1-propanol in the place of (*R*)-(-)-1-amino-2-propanol, 2.70 g (0.015 mol) of diglycolyl chloride, 3.04 g (0.03 mol) of triethylamine and 5.50 g (0.15 mol) of $LiAlH_4$. The crude product was purified by chromatography on silica gel using

$CH_3OH/CHCl_3$ (1/5) as eluant to give 1.61 g (29%) of **10** as a yellow oil; $[\alpha]_D$+14.1 (c = 0.23, $CHCl_3$); IR (neat) 3448, 2954, 1678, 1648, 1531, 1384, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 6H), 2.87-3.10 (m, 6H), 3.40-3.70 (b, 4H, disappeared on addition of D_2O), 3.70 (t, 4H), 4.95 (d, 2H), 7.31-7.43 (m, 10H); MS *m/e* 372 (M^+). A satisfactory elemental analysis was obtained for **5**, a derivative of **10**.

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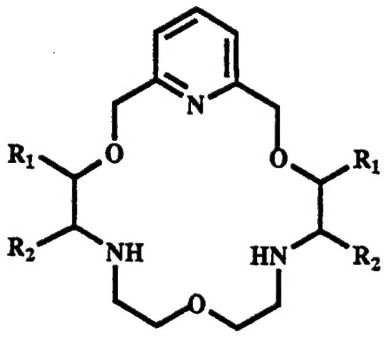
Figure and Scheme Captions:

Figure 1. New Chiral Diazapyridino-18-crown-6 Ligands.

Scheme 1. Preparation of New Chiral Ligands

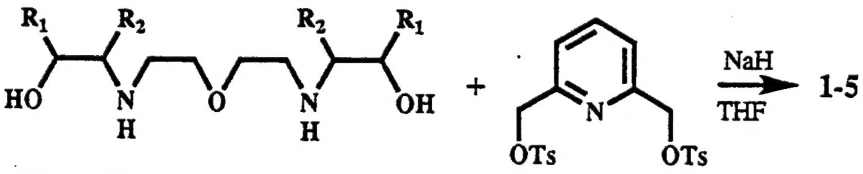
Scheme 2. Preparation of Chiral Starting Materials

Figure 1



1, $R_1 = CH_3$; $R_2 = H$ (*R,R*)
2, $R_1 = H$; $R_2 = CH_3$ (*R,R*)
3, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*R,R*)
4, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*S,S*)
5, $R_1 = Ph$; $R_2 = CH_3$ (*4R,5S,13S,14R*)

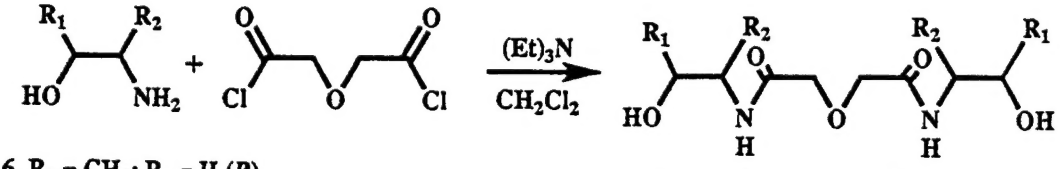
Scheme I



6, $R_1 = CH_3$; $R_2 = H$ (*R,R*)
7, $R_1 = H$; $R_2 = CH_3$ (*R,R*)
8, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*R,R*)
9, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*S,S*)
10, $R_1 = Ph$; $R_2 = CH_3$ (1*R*, 2*S*, 10*S*, 11*R*)

Scheme II

A.

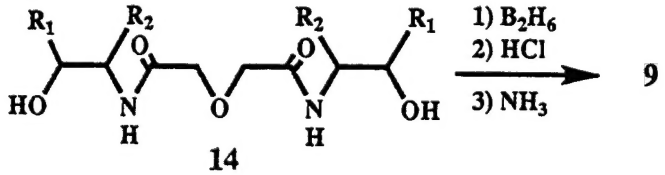


16, $R_1 = CH_3$; $R_2 = H$ (*R*)
17, $R_1 = H$; $R_2 = CH_3$ (*R*)
18, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*R*)
19, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*S*)
20, $R_1 = Ph$; $R_2 = CH_3$ (1*R*, 2*S*)

11, $R_1 = CH_3$; $R_2 = H$ (*R*)
12, $R_1 = H$; $R_2 = CH_3$ (*R*)
13, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*R*)
14, $R_1 = H$; $R_2 = C_6H_5CH_2$ (*S*)
15, $R_1 = Ph$; $R_2 = CH_3$ (1*R*, 2*S*)

$LiAlH_4$, THF → 6-8 and 10

B.



14

1) B_2H_6
2) HCl
3) NH_3
→ 9